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Attorney Docket No. 208250

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Ho et al.

Art Unit: Unassigned

U.S. National Phase of PCT/US99/16199

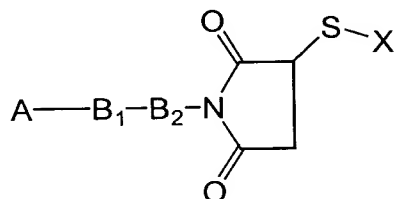
Examiner: Unassigned

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For: WATER-SOLUBLE DRUGS AND  
RELATED COMPOSITIONS AND  
METHODS OF PREPARING SAME

PENDING CLAIMS AS OF JANUARY 17, 2001

63. A water-soluble compound of the formula



wherein:

A is a water-insoluble drug;

B<sub>1</sub> and B<sub>2</sub> together are a spacer moiety; and

X is a polar moiety;

or a pharmaceutically acceptable salt of said compound.

64. The compound of claim 63, wherein

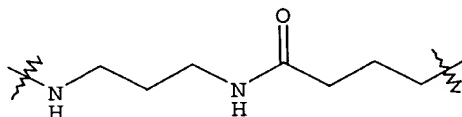
B<sub>1</sub> is selected from the group consisting of a methylenyl, an amido, -N=, an amino, and a thiol maleimido, and

B<sub>2</sub> is selected from the group consisting of a C<sub>1</sub>-C<sub>19</sub> alkylamido, a C<sub>1</sub>-C<sub>19</sub> alkyl, a C<sub>2</sub>-C<sub>19</sub> alkenyl, a C<sub>2</sub>-C<sub>19</sub> alkynyl, a C<sub>1</sub>-C<sub>19</sub> hydroxyalkyl, a C<sub>1</sub>-C<sub>19</sub> alkyl carbamoyl, a C<sub>1</sub>-C<sub>19</sub> alkylcarbonyl, and an aralkyl, any of which can be further substituted with one or more substituents, which can be the same or different, selected from the group consisting of a nitro, a halo, an azido, a hydroxy, an amido, and an amino group.

65. The compound of claim 64, wherein

B<sub>2</sub> is selected from the group consisting of a C<sub>1</sub>-C<sub>7</sub> alkylamido, a C<sub>1</sub>-C<sub>7</sub> alkyl, a C<sub>2</sub>-C<sub>7</sub> alkenyl, a C<sub>2</sub>-C<sub>7</sub> alkynyl, a C<sub>1</sub>-C<sub>7</sub> hydroxyalkyl, a C<sub>1</sub>-C<sub>7</sub> alkyl carbamoyl, a C<sub>1</sub>-C<sub>7</sub> alkylcarbonyl, and an aralkyl, any of which can be further substituted with one or more substituents, which can be the same or different, selected from the group consisting of a nitro, a halo, an azido, a hydroxy, an amido and an amino group.

66. The compound of claim 65, wherein said spacer moiety has the structure



67. The compound of claim 63, wherein said polar moiety is an amino acid, a peptide, a polypeptide, or a protein.

68. The compound of claim 67, wherein said polar moiety is L-cysteine.

69. The compound of claim 63, wherein said polar moiety is ionic at neutral pH.

70. The compound of claim 69, wherein said compound is zwitterionic at neutral pH.

71. The compound of claim 63, wherein said water-insoluble drug is a macrolide or an ansamacrolide.

72. The compound of claim 63, wherein said drug is geldanamycin or a derivative thereof.

73. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound of claim 63.

74. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound of claim 64.

75. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound of claim 65.

76. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound of claim 66.

77. A method of treating cancer in a mammal, which method comprises administering to a mammal having cancer an anticancer effective amount of a compound of claim 63, whereupon the cancer in the mammal is treated.

78. A method of treating cancer in a mammal, which method comprises administering to a mammal having cancer an anticancer effective amount of a compound of claim 64, whereupon the cancer in the mammal is treated.

79. A method of treating cancer in a mammal, which method comprises administering to a mammal having cancer an anticancer effective amount of a compound of claim 65, whereupon the cancer in the mammal is treated.

80. A method of treating cancer in a mammal, which method comprises administering to a mammal having cancer an anticancer effective amount of a compound of claim 66, whereupon the cancer in the mammal is treated.

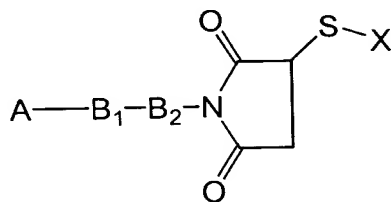
81. A method of rendering soluble in water a water-insoluble drug, which method comprises:

(i) providing a water-insoluble drug comprising a side-chain that can react with a bifunctional linking molecule;

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(ii) contacting said water-insoluble drug with said bifunctional linking molecule to obtain a first derivative comprising a maleimide side-chain; and

(iii) contacting said first derivative with a thio containing polar moiety (X-SH) to obtain a water-soluble compound of the formula



wherein:

A is a water-insoluble drug;

B<sub>1</sub> and B<sub>2</sub> together are a spacer moiety; and

X is a polar moiety;

or a pharmaceutically acceptable salt of said compound.

82. The method of claim 81, wherein

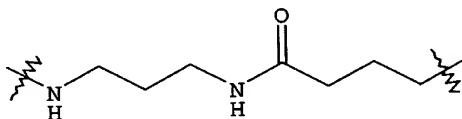
B<sub>1</sub> is selected from the group consisting of methylenyl, an amido, -N=, an amino, and a thiol maleimido, and

B<sub>2</sub> is selected from the group consisting of a C<sub>1</sub>-C<sub>19</sub> alkylamido, a C<sub>1</sub>-C<sub>19</sub> alkyl, a C<sub>2</sub>-C<sub>19</sub> alkenyl, a C<sub>2</sub>-C<sub>19</sub> alkynyl, a C<sub>1</sub>-C<sub>19</sub> hydroxyalkyl, a C<sub>1</sub>-C<sub>19</sub> alkyl carbamoyl, a C<sub>1</sub>-C<sub>19</sub> alkylcarbonyl, and an aralkyl, any of which can be further substituted with one or more substituents, which can be the same or different, selected from the group consisting of a nitro, a halo, an azido, a hydroxy, an amido and an amino group.

83. The method of claim 82, wherein

B<sub>2</sub> is selected from the group consisting of a C<sub>1</sub>-C<sub>7</sub> alkylamido, a C<sub>1</sub>-C<sub>7</sub> alkyl, a C<sub>2</sub>-C<sub>7</sub> alkenyl, a C<sub>2</sub>-C<sub>7</sub> alkynyl, a C<sub>1</sub>-C<sub>7</sub> hydroxyalkyl, a C<sub>1</sub>-C<sub>7</sub> alkyl carbamoyl, a C<sub>1</sub>-C<sub>7</sub> alkylcarbonyl, and an aralkyl, any of which can be further substituted with one or more substituents, which can be the same or different, selected from the group consisting of a nitro, a halo, an azido, a hydroxy, an amido, and an amino group.

84. The method of claim 83, wherein said spacer moiety has the structure



85. The method of claim 81, wherein step (i) comprises contacting a water-insoluble drug with a modifying agent to provide a water-insoluble drug comprising a side-chain that can react with a bifunctional linking molecule.

86. The method of claim 85, wherein said water-insoluble drug comprises a methoxyaryl moiety that can react with said modifying agent, and said modifying agent comprises a primary amine, whereupon reacting said water-insoluble drug with said modifying agent, a demethoxy derivative of said water-insoluble drug comprising a portion of said modifying agent as a side chain is provided and wherein said portion of said modifying agent can react with said bifunctional linking molecule.

87. The method of claim 85, wherein said modifying agent is a diaminoalkane.

88. The method of claim 81, wherein said thio containing polar moiety is an amino acid, a polypeptide or a protein.

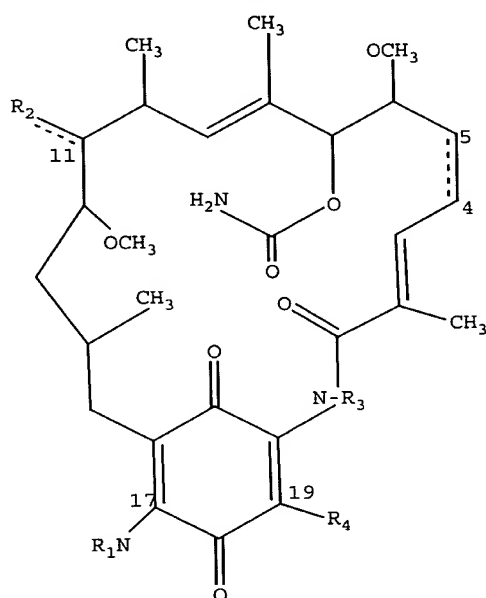
89. The method of claim 81, wherein said water-insoluble drug is a macrolide or an ansamacrolide.

90. The method of claim 81, wherein said water-insoluble drug is geldanamycin or a derivative of geldanamycin.

91. The method of claim 81, wherein said bifunctional linking molecule is selected from the group consisting of N-γ-maleimidobutyryloxysuccinimide ester (GMBS), sulfo-N-γ-maleimidobutyryloxysuccinimide ester (sulfo-GMBS), *m*-maleimidobenzoyl-N-hydroxysuccinimide ester (MBS), *m*-maleimidobenzoyl-N-

hydroxysulfosuccinimide ester (sulfo-MBS), succinimidyl 4-*[p*-maleimidophenyl]butyrate (SMPB), sulfosuccinimidyl 4-*[p*-maleimidophenyl]butyrate (sulfo-SMPB), succinimidyl 4-[N-maleimidomethyl]cyclohexane-1-carboxylate (SMCC), sulfosuccinimidyl 4-[N-maleimidomethyl]cyclohexane-1-carboxylate (sulfo-SMCC), 4-[N-maleimidomethyl]-cyclohexane-1-carboxylhydrazide-HCl (M2C2H), and 4-[4-maleimidophenyl]-butyric acid hydrazide-HCl (MPBH).

92. A water-soluble compound of the formula



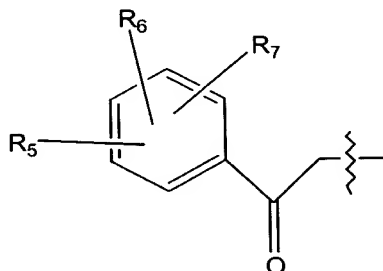
or a pharmaceutically acceptable salt thereof, wherein:

R<sub>1</sub> is a charged moiety at neutral pH,

R<sub>2</sub> is a halo or an -OR<sub>8</sub> when there is a single bond between R<sub>2</sub> and the carbon at position 11, wherein R<sub>8</sub> is selected from the group consisting of hydrogen, a C<sub>1</sub>-C<sub>8</sub> alkylamido, a C<sub>1</sub>-C<sub>8</sub> alkyl, a C<sub>2</sub>-C<sub>8</sub> alkenyl, a C<sub>2</sub>-C<sub>8</sub> alkynyl, a C<sub>1</sub>-C<sub>8</sub> hydroxyalkyl, a C<sub>1</sub>-C<sub>8</sub> alkyl carbamoyl, a C<sub>1</sub>-C<sub>8</sub> alkylcarbonyl, and an aralkyl, any of which R<sub>8</sub> groups can be further substituted with one or more substituents, which can be the same or different, selected from the group consisting of a nitro, a halo, an azido, a hydroxy, an amido and an amino groups, or

R<sub>2</sub> is oxo (=O) or oximino (=NOH) when there is a double bond between R<sub>2</sub> and the carbon at position 11,

R<sub>3</sub> is selected from the group consisting of hydrogen and a group of the formula



wherein R<sub>5</sub>, R<sub>6</sub>, and R<sub>7</sub> are each independently selected from the group consisting of hydrogen, a halo, an azido, a nitro, a C<sub>1</sub>-C<sub>8</sub> alkyl, a C<sub>1</sub>-C<sub>8</sub> alkoxy, an aryl, a cyano, and an NR<sub>10</sub>R<sub>11</sub>R<sub>12</sub>, wherein R<sub>10</sub>, R<sub>11</sub>, and R<sub>12</sub> are each independently selected from the group consisting of hydrogen and a C<sub>1</sub>-C<sub>3</sub> alkyl,

R<sub>4</sub> is selected from the group consisting of hydrogen, a halo, a C<sub>1</sub>-C<sub>8</sub> alkylamino, and a C<sub>1</sub>-C<sub>8</sub> dialkylamino, and

the bond between the carbons at positions 4 and 5 can be a single bond or a double bond.

93. The compound of claim 92, wherein R<sub>1</sub> is an aliphatic moiety which optionally comprises an aryl ring, wherein said aliphatic moiety is substituted by one or more charged moieties, which can be the same or different, selected from the group consisting of carbamate, carbonate, carboxylate, phosphamate, phosphate, phosphonate, pyrophosphate, triphosphate, sulfamate, sulfate, sulfonate, a C<sub>1</sub>-C<sub>8</sub> monoalkylamine that is protonated at neutral pH, a C<sub>1</sub>-C<sub>4</sub> dialkylamine that is protonated at neutral pH, and a C<sub>1</sub>-C<sub>4</sub> trialkylammonium.

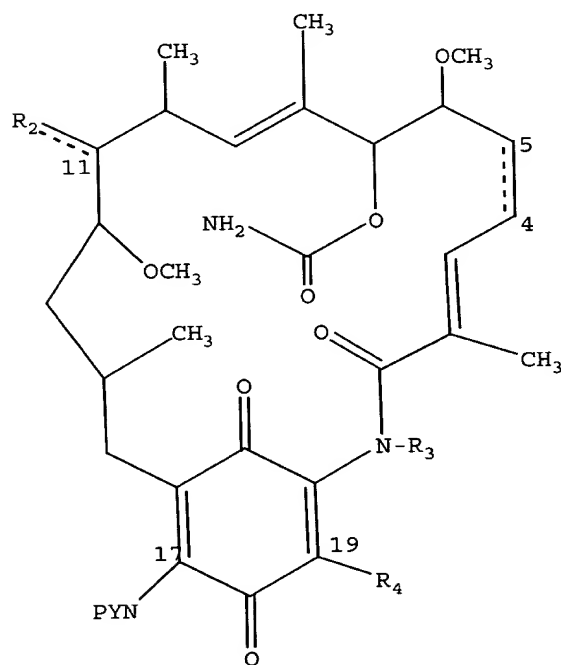
94. The compound of claim 93, wherein R<sub>1</sub> is selected from the group consisting of a C<sub>1</sub>-C<sub>19</sub> alkylamido, a C<sub>1</sub>-C<sub>19</sub> alkyl, a C<sub>2</sub>-C<sub>19</sub> alkenyl, a C<sub>2</sub>-C<sub>19</sub> alkynyl, a C<sub>1</sub>-C<sub>19</sub> hydroxyalkyl, a C<sub>1</sub>-C<sub>19</sub> alkyl carbamoyl, a C<sub>1</sub>-C<sub>19</sub> alkylcarbonyl, and an aralkyl, any of which can be further substituted with one or more substituents, which can be the same or different, selected from the group consisting of a nitro, a halo, an azido, a hydroxy, an amido, and an amino group.

95. The compound of claim 94, wherein  $R_1$  is selected from the group consisting of a  $C_1$ - $C_7$  alkylamido, a  $C_1$ - $C_7$  alkyl, a  $C_2$ - $C_7$  alkenyl, a  $C_2$ - $C_7$  alkynyl, a  $C_1$ - $C_7$  hydroxyalkyl, a  $C_1$ - $C_7$  alkyl carbamoyl, a  $C_1$ - $C_7$  alkylcarbonyl, and a monocarbocyclic aralkyl any of which can be further substituted with one or more substituents, which can be the same or different, selected from the group consisting of a nitro, a halo, an azido, a hydroxy, an amido, and an amino group.

96. The compound of claim 94, wherein said aliphatic moiety comprises a moiety selected from the group consisting of a nucleoside, a saccharide, and an amino acid.

97. The compound of claim 92, wherein  $R_1$  is zwitterionic at neutral pH.

98. A water-soluble compound of the formula



or a pharmaceutically acceptable salt thereof, wherein:

Y is a spacer group, said spacer group comprising a thio ether,

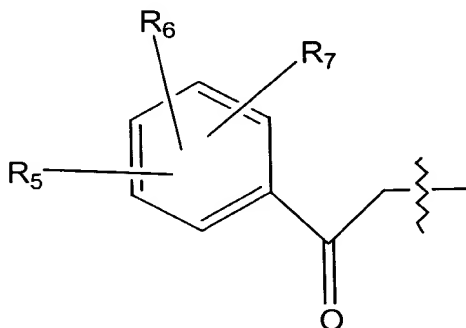
P is a polypeptide or a protein that selectively binds to the surface of a mammalian cell,



$R_2$  is a halo or an  $-OR_8$  when there is a single bond between  $R_2$  and the carbon at position 11, wherein  $R_8$  is selected from the group consisting of hydrogen, a  $C_1-C_8$  alkylamido, a  $C_1-C_8$  alkyl, a  $C_2-C_8$  alkenyl, a  $C_2-C_8$  alkynyl, a  $C_1-C_8$  hydroxyalkyl, a  $C_1-C_8$  alkyl carbamoyl, a  $C_1-C_8$  alkylcarbonyl, and an aralkyl, any of which  $R_8$  groups can be further substituted with one or more substituents, which can be the same or different, selected from the group consisting of a nitro, a halo, an azido, a hydroxy, an amido, and an amino group, or

$R_2$  is oxo ( $=O$ ) or oximino ( $=NOH$ ) when there is a double bond between  $R_2$  and the carbon at position 11,

$R_3$  is selected from the group consisting of hydrogen and a group of the formula

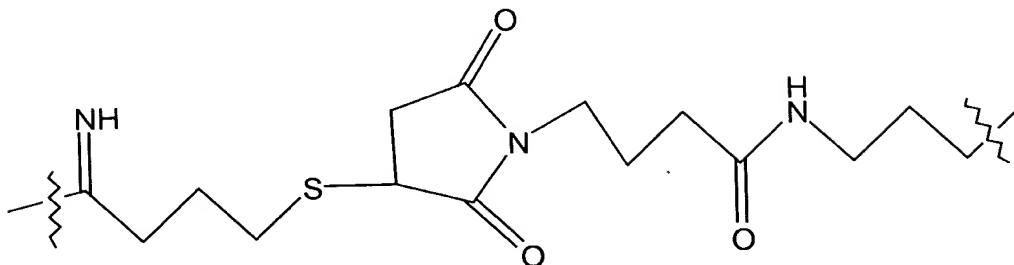


wherein  $R_5$ ,  $R_6$ , and  $R_7$  are each independently selected from the group consisting of hydrogen, a halo, an azido, a nitro, a  $C_1-C_8$  alkyl, a  $C_1-C_8$  alkoxy, an aryl, a cyano, and an  $NR_{10}R_{11}R_{12}$ , wherein  $R_{10}$ ,  $R_{11}$ , and  $R_{12}$  are each independently selected from the group consisting of hydrogen and a  $C_1-C_3$  alkyl,

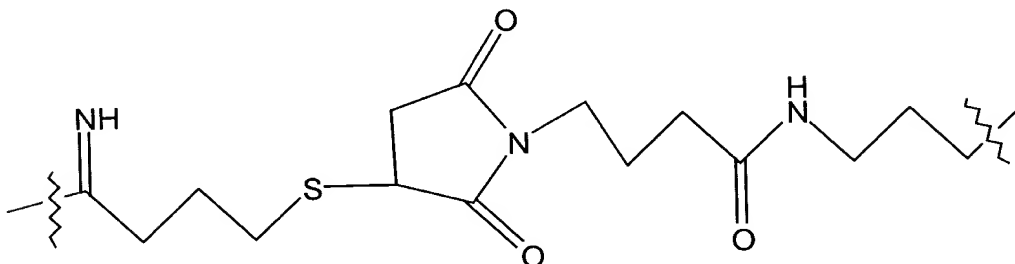
$R_4$  is selected from the group consisting of hydrogen, a halo, a  $C_1-C_8$  alkylamino, and a  $C_1-C_8$  dialkylamino, and the bond between the carbons at positions 4 and 5 can be a single bond or a double bond.

99. The compound of claim 98, wherein P comprises a lysine and Y is bonded to P via said lysine.

100. The compound of claim 98, wherein Y is



101. The compound of claim 99, wherein Y is



102. The compound of claim 98, wherein said protein or polypeptide is an antibody, or an antigenically reactive fragment thereof.

103. The compound of claim 102, wherein said antibody is humanized.

104. A method of treating cancer in a mammal, which method comprises administering to a mammal having cancer an anticancer effective amount of a compound comprising a polypeptide or protein covalently bonded to 17-demethoxy-17-amino-geldanamycin or a derivative thereof, wherein said polypeptide or protein binds to the surface of a cancer cell and whereupon said cancer is treated.

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105. The method of claim 104, wherein said polypeptide or protein is bonded to said 17-demethoxy-17-amino-geldanamycin or a derivative thereof via a spacer moiety comprising a thio ether.

106. The method of claim 104, wherein said compound is internalized by said cancer cell.

105. The method of claim 104, wherein said polypeptide or protein is bonded to said 17-demethoxy-17-amino-geldanamycin or a derivative thereof via a spacer moiety comprising a thio ether.